REMARKS

Claims 1-6, 8-14, 17-19, 48, 50, and 58-61 are pending in the instant application. Claims 60 and 61 have been amended to incorporate the text of Claim 1 and modified to independent claims. Therefore, no new matter has been added by this amendment.

I. STATEMENT OF THE SUBSTANCE OF THE INTERVIEW

Applicants thank Examiner Yong Soo Chong for the courtesies extended during the telephonic interview of June 24, 2008. Also participating in the Interview was Dr. Anthony Cerami, an inventor of the instant application, and Frederick J. Hamble, Esq., Applicants' representative.

During the Interview an overview of the invention was presented. In summary, the inventor provided an overview of current methods of vaccination and described the inventors' discovery that the design of the virtual lymph node device produced an unexpectedly robust response to an antigen. The inventor explained that many of the vaccines in use today are composed of viruses and/or bacteria that have been killed or whose virulence has been attenuated in some way. Because of the risks of incomplete activation and reversion to full virulence, most vaccines currently under development are composed of synthetic, recombinant or highly purified subunit antigens that are generally considered safer than whole-inactivated or live attenuated vaccines. However, these vaccines containing purified subunit antigens are often less immunogenic than traditional vaccines, and therefore require the use of adjuvants which amplify the immune response.

Unfortunately, while a number of adjuvants such as Ribi and Freund's complete and incomplete are successfully used in animal models, these adjuvants have not been approved for human use due to their systemic toxicities. The inventor noted that a method of amplifying immune responses with the effectiveness but without the associated toxicities of conventional adjuvants was needed.

The virtual lymph node device of the current invention is capable of eliciting an immune response as good or better than conventional adjuvants. The inventor noted that the device achieved this efficacy by mimicking the structure and function of a lymph node, the highly specialized lymphoid organ where antigen is processed and presented to B and T lymphocytes. The virtual lymph node emulates the lymph node by providing for a porous matrix containing antigen surrounded by a diffusion barrier -- a perforated but otherwise impermeable container to permit the immune cells to enter the device while maintaining within the device a high concentration of antigen and cytokines and chemokines associated with the immune response. The inventor noted that this design: (1) attracts all the critical elements of the immune system including B, T, and professional antigen presenting cells into a single site, (2) increases the biological and immunological half-lives of vaccine antigens, (3) activate immune cells, (4) induce and maintain high levels of immunomodulatory cytokines, and (5) provide an environment that facilitates the interaction of T cells and antigen-loaded antigen presenting cells. The inventor further noted that this was done without inducing the systemic toxicities associated with effective adjuvants.

The outstanding rejections under 35 U.S.C. § 103(a), obviousness in light of Barr et al. (US Patent 5,593,697) and Andrianov et al. (US Patent 5,529,777), made in the Office Action dated February 14, 2008 (the "Office Action") were discussed. Applicants asserted that neither Barr nor Andrianov discussed perforations in the device at the time of implantation or perforation of the number or diameter disclosed by the current application. The possibility of amending the independent claim to incorporate the number and diameter limitations for perforations in the container of the device was discussed.

The Examiners also indicated that evidence of unexpected results obtained from the device may be helpful as well in overcoming the obviousness rejection.

This Amendment, the diagram of the VLN device provided to the Examiner for the interview submitted herewith, and the remarks herein reflect the discussion during the Interview.

1. REJECTION FOR DOUBLE PATENTING

Applicants thank the Examiner for acknowledging their request to hold the double patenting rejections in abeyance until allowable subject matter is identified.

2. REJECTION FOR OBVIOUSNESS UNDER 35 U.S.C. § 103(a) SHOULD BE WITHDRAWN

Claims 1-6, 8-14, 17-19, 48, 50, and 58-61 were rejected under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 5,593,697 by Barr et al. ("Barr") in view of U.S. Patent No. 5,529,777 by Andrianov et al. ("Andrianov"). In particular, the Examiner asserts that Barr discloses a pharmaceutical implant with a water insoluble coat made of polymeric material that is functionally equivalent to the device of the present invention. The Examiner further argues that the present invention is obvious over Barr in view of Andrianov, because Andrianov teaches encapsulating hybridoma cells in the microspheres.

Applicants believe that Claims 1-6, 8-14, 17-19, 48, 50, and 58-61 are non-obvious for the reasons discussed below.

2.1 The Legal Standard

A finding of obviousness requires that "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. §103(a). To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the prior art references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. M.P.E.P. 2143.

In its recent decision addressing the issue of obviousness, *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 USPQ2d 1385 (2007), the Supreme Court affirmed that it

is "important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does . . . because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." *KSR*, 127 S.Ct. at 1741, 82 USPQ2d at 1396. Thus, consistent with the principles enunciated in *KSR*, a *prima facie* case of obviousness can be established by showing a suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference *and* to carry out the modification with a reasonable expectation of success, viewed in light of the prior art.

Both the suggestion and the reasonable expectation of success must be found in the prior art and *not* be based on the applicant's disclosure. *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988). With regard to the final point, the *KSR* Court citing *Graham*, upheld the principle of *avoiding hindsight bias* and cautioned courts to *guard against reading into the prior art the teachings of the invention in issue.* 127 S.Ct. at 1742, 82 USPQ at 1397.

In addition, in determining obviousness objective evidence of nonobviousness may be considered. See *Graham et al. v. John Deere Co. of Kansas City et al.*, 383 U.S. 1 (1966). In particular factors such as: commercial success, long-felt but unsolved needs, failure of others, skepticism and disbelief (*Environmental Designs, Ltd. v. Union Oil Co. of Cal.*, 713 F.2d 693, 697-98, 218 USPQ 865, 869 (Fed. Cir. 1983)), copying, praise, unexpected results, and industry acceptance as indicators of nonobviousness (*Allen Archery, Inc. v. Browning Mfg. Co.*, 819 F.2d 1087, 1092, 2 USPQ2d 1490, 1493 (Fed. Cir. 1987)).

2.2 The Invention

The present invention relates to a novel implantable device containing an antigen that is designed to attract cells of the immune system to the antigen in a controlled fashion. Perforations in the container component of the device create a diffusion barrier that

maintains optimal levels of antigen, immune cell secretory products and immune cells within the device. Page 14, lines 2-7. These perforations are designed, to restrict the passive diffusion of small molecules, such as antigens, but permit the active movement of immune and other cells into and out of the device. Page 19, lines 14-18. The diffusion barrier is maintained due to the size and number of perforations in otherwise impermeable container. Page 22, line 20 to page 23, line 4. This generates a localized system in which the immune response can propagate similar to that present in a lymph node and thereby results in an enhanced immune response.

In addition to the data presented within the current application, the Applicants have tested the device of the current invention in a human clinical trial, the details of which are set forth in the attached Declaration of Carla Cerami Hand. In these clinical trials regarding vaccination against influenza, the cells of volunteers implanted with the device containing the influenza vaccine elicited a cellular immune response about three times greater than the cells of volunteers that received only the influenza vaccine. This result was particularly unexpected given that 90 times less influenza vaccine was loaded into the device than was administered to the volunteers that received only the influenza vaccine.

2.3 The Claimed Invention Is Non-Obvious

Barr discloses a pharmaceutical implant for the delayed release of active agents with a water insoluble coat made of polymeric material equivalent to the material of the device of the present invention. Thus, the Examiner maintains that Barr device must be functionally equivalent to the present invention – *i.e.*, that the Barr device will attract cells of immune system to encounter the antigen within the device and modulate the immune response — because a composition and its properties are inseparable.

The Applicants have respectfully disagreed with the Examiner and still maintain that the current invention is not obvious in light of Barr. Applicants maintain that Barr lacks an essential element of the claims – perforations in the outer layer of the device. This outer layer, called the "container," contains perforations in otherwise impermeable

material. See page 14, line 2-7. The outer layer of the Barr device, called "film coating," does not feature any perforations and, as a result, is completely impermeable prior to rupture. See Col. 5, lines 1-5.

The benefits of the current invention are derived from its structural design as opposed to the chemical composition of its components. It is the very structural differences between the device of the invention and the Barr device – the presence of perforations in the device of the present invention and the absence in the Barr device – that distinguish the two devices. These perforations give the instant invention the unique property of allowing immune cells to enter the device and encounter the antigen within the device, and thus the device of the current invention provides a localized environment in which the immune response may propagate similar to a lymph node.

However, the Examiner now contends that Barr also teaches polymers that have holes in the coating thus forming pores which then permit release based upon the disclosure found at column 6, lines 26-49 of Barr.

The Applicants disagree with the Examiner's contention. The disclosure within Barr relied upon by the Examiner does not teach the use of pores within the Barr device. The disclosure merely explains why Barr teaches the use of a film coating comprised of ethylcellulose and a copolymer of glyolic and lactic acid (PLGA) as opposed to merely using PLGA. In particular, Barr notes that "PLGA has a low glass transition temperature, and is difficult to film coat onto implant cores using conventional film coating equipment, as the film becomes tacky causing the cores to aggregate and the separate which leads to picking (holes forming in the film)." Col. 6, lines 28-32. It is evident that Barr does not consider this as being desirable given that it goes onto state that a blend of ethylenecellulose and PLGA has a higher glass transition temperature and therefore leads to a higher quality film. Thus, contrary to the Examiner's assertion Barr does not disclose the use of perforations in the film coating of the device but explains that picking (holes

forming in the film) is an undesirable consequence of using a film of 100% PLGA.[1] Thus, the Applicants maintain that Barr does not teach a device having perforations.

Further, currently amended claims 60 and 61 indicate that the perforations in the device are of a certain size (1/16 to 1/32 of an inch in diameter) and number (10 perforations per centimeter of container), respectively. The Examiner objected to previous claims 60 and 61, alleging that the size and number of perforations to optimize release of the active agent would merely be a matter of optimization for one of ordinary skill in the art in light of the Barr disclosure.

Applicants disagree with the Examiner's contention. Applicants maintain that one of ordinary skill in the art would have no motivation to modify the Barr device in accordance with the device of the claimed invention.[2] Not only does Barr fail to suggest or provide motivation to incorporate perforations into the film coating, but such perforations would be contrary to the goals of Barr. The goal of Barr's invention is to provide a delayed pulsed release of antigen. Col. 3, lines 11-15. The bilayer film coating of the Barr reference forms an impermeable barrier to antigen until the failure of the inner film coating layer leads to rupture of the outer film coating layer. Col. 5, lines 2-14. Presence of perforations would frustrate the purpose of the Barr's invention by facilitating the flow of physiological fluid inside the Barr's device resulting in an immediate release of the antigen, rather than delayed release, of antigen.

Further, even if Barr taught perforations, which the Applicants maintain that Barr does not, one of ordinary skill in the art would not arrive at the size and number of perforations based upon the Barr disclosure because the goals of Barr and the current invention are inapposite to one another. Barr seeks a delayed release of antigen from the device and one of ordinary skill in the art would be motivated to optimize the size and number of perforations for the release of antigen from the Barr device as asserted by the

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[1] Andrianov echoes the disadvantages of using PLGA as a film coating. Andrianov notes that the process of coating with PLGA utilizes shear forces and organic solvents can damage the immunogens sought to be encapsulated. US Patent 5,529,777, Col. 4, lines 23-45.

[2] Note that Barr, Example 6, discusses coating the implant with the antigen/adjuvant and a water soluble polymer to achieve an immediate release of the antigen/adjuvant as opposed to using holes or perforations.

Examiner. However, the current invention teaches that the perforations should be of a size and number to permit the ingress and egress of immune cells but to prevent a substantial release of the antigen and co-stimulatory factors from the device. Thus, the goals of Barr and the current invention are diametrically opposed and one of ordinary skill seeking to optimize the size and number or perforations to achieve the goals of Barr would design perforations optimized for the release of antigen and, therefore, inappropriate for the current invention.

Moreover, the method of the present invention is not obvious over Barr in view of Andrianov. Andrianov teaches the use of antigens mixed with a polymer solution for the controlled release of antigen at the target surface. Col. 4, line 66 to Col. 5, line 2; Col. 5, lines 23-31. Andrianov neither suggests an impermeable outer coating layer nor perforations in the polymer microspheres. Indeed, such perforations would serve no purpose in the delayed controlled release formulation taught by Andrianov. Further, Andrianov teaches that the microcapsules have a diameter of between one and 200 microns and could not suggest the incorporation of perforations of a size or number claimed in claims 60 and 61 given that a perforation 1/16 (1587.5 microns) to 1/32 (793.75 microns) of an inch in diameter would be larger than the microparticles disclosed by Andrianov.

Further, the non-obviousness of the device is illustrated by the unexpected efficacy of the device of the current invention. As noted above, the use of the device to vaccinate volunteers against influenza in a clinical trial demonstrated that cellular immune response achieved in volunteers that were immunized using the device was about three times greater than that of volunteers that received only the influenza vaccine. This result was particularly unexpected given that 90 times less influenza vaccine was loaded into the device than was administered to the volunteers that received only the influenza vaccine. Further, this result was achieved via a single dose regime with the device. In comparison, as shown in Example 5 the Barr device only elicited a similar immune response to a delayed administration CLA toxoid regime. As noted within, Table 3, the delayed release device of Barr used with an immediate release device elicited an immune response similar

to two conventional liquid dose immunizations of the CLA toxoid administered 21 days apart. *See* col. 13, lines 40-43. Thus, the devices of the current invention unexpectedly achieved an enhanced response to an antigen when administered at a substantially lower dose than would have been administered as a conventional liquid dose.

The references cited by the Examiner do not suggest or provide motivation for the presently claimed invention, let alone to do so with an expectation of success. The devices of Barr and Andrianov induce an immune response in a manner different than the device of the present invention. Both devices of Barr and Andrianov serve as delayed release formulations, and perforations in the polymer material would either frustrate the purpose of such devices or serve no purpose at all. In contrast, the novel device of the present invention is designed to enable contact between immune cells and antigen within the device, and perforations in the container component of the device enable such contact. Given the difference in purpose served by the devices of Barr and Andrianov and the device of the present invention, the introduction of perforations would not have been obvious to one of ordinary skill in the art at the time the invention was made.

In addition, the additional limitations relating to the structural features of the perforations, specifically their size and number, in the container component of the device are not disclosed in either Barr or Andrianov, nor are they obvious over either reference or the combination of references.

The Examiner acknowledges that Barr does not teach the use of the device for generating hybridomas. However, the Examiner relies upon Andrianov to argue that it would have been obvious to one of ordinary skill in the art to use the current invention to make hybridomas. The Examiner further argues that one of ordinary skill in the art would remove a device in accordance with Barr and prepare hybridomas in accordance with Andrianov.

However, neither Barr nor Andrianov teach nor motivate one of ordinary skill in the art each of the limitations of previous claim 48. In particular, claim 48 states that the immune cells are harvested from the device. Both Barr and Andrianov teach that the immune response is initiated by the release of the antigen from the device. *See* Barr, col.

5, lines 16-18 and Andrianov, col. 16, lines 18-22. One of ordinary skill of art would recognize that the immune response would occur at the site of the antibody, the stimulus for the immune response. Thus, with the release of antibody from the devices of Barr and Andrianov one of ordinary skill in the art would have no motivation for removing the devices in the hopes of harvesting immune cells given their recognition that the immune cells would converge on the antigens released from the device. For example, in Example 7 and Table 6 of Andrianov, which the Examiner relies upon for an illustration of harvesting of antibodies, these were not harvested from the microcapsules of Andrianov but from the sera of the mice, col. 24, lines 15-17. Further, despite the Examiner's numerous assertions otherwise, Barr does not disclose the presence of immune cells within the Barr device. Similar to Andrianov, Barr determined the immune response due to the delayed release of antigen from the Barr device by sampling the sera of the test mice as opposed to the Barr device. See Examples 4 and 5. Thus, one of ordinary skill in the art, based on the disclosures of Andrianov or Barr, would not think to remove the Barr device and attempt to harvest immune cells from the device given that the antigen has been released from the device and that the immune response would be ongoing in the tissues surrounding the device.

Further, Andrianov fails to teach or suggest a method of preparation of a hybridoma for the production of monoclonal antibodies against a specific antigen. The Examiner points out that Andrianov discloses encapsulating hybridoma cells in the microspheres. Example 1. However, the reference to hybridomas in Example 1 is illustrative that the polymers used for microencapsulation are non-toxic because hybridomas were able to propagate within microcapsule, *see* col. 15, lines 34-43, not as a method of manufacturing hybridomas. Further, contrary to the Andrianov reference, the method of present invention does not include encapsulating of hybridoma cells in the miscrospheres or in the device of the present invention. Instead, the present invention includes immunizing a mammal with an antigen contained within the device, followed by harvesting of the immune cells from the device for the subsequent production of antigen-specific hybridomas. Page 17, lines 18-23. Importantly, encapsulating of hybridoma cells in the microspheres or in the device would not achieve the purpose of the present

invention, which is to generate a hybridoma for the production of monoclonal antibodies against a specific antigen. Therefore, the combination of Barr and Andrianov references will not render the current invention obvious.

Therefore, the prior art references, Barr and Andrianov, alone or taken together, neither teach nor suggest all the claim limitations of the present invention. Nor was there knowledge generally available to one of ordinary skill in the art at the time the invention was made, to modify Barr and Andrianov to include perforations in the outer layer of the device, and to carry out the modification with a reasonable expectation of success. Thus, the current invention would not have been obvious to one of ordinary skill in the art.

In view of the remarks above, the Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 103(a). In the alternative, the Applicants respectfully request that the Examiner support the conclusion of obviousness based on knowledge within the level of ordinary skill in the art by an affidavit pursuant to rule 37 CFR 1.104(d)(2).

CONCLUSION

Entry of the foregoing remarks and amendment into the record of the above-identified application is respectfully requested. Applicants estimate that the remarks and amendment made herein now place the pending claims in condition for allowance. If any issues remain in connection herewith, the Examiner is invited to telephone the undersigned to discuss the same.

Respectfully submitted,

Date: August 14, 2008

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